PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR TAMIFLU (OSELTAMIVIR PHOSPHATE)

This is a summary of the risk management plan (RMP) for Tamiflu. The RMP details important risks of Tamiflu, how these risks can be minimized, and how more information will be obtained about Tamiflu risks and uncertainties (missing information).

Tamiflu's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Tamiflu should be used.

This summary of the RMP for Tamiflu should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Tamiflu RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Tamiflu is authorized for treatment and prevention of influenza. It contains oseltamivir as the active substance and it is given by oral administration.

Further information about the evaluation of Tamiflu's benefits can be found in Tamiflu's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Tamiflu, together with measures to minimize such risks and the proposed studies for learning more about Tamiflu risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Tamiflu is not yet available, it is listed under 'missing Information' below.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Tamiflu are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tamiflu. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Development of oseltamivir-induced viral resistance
Important potential risks	Exposure during pregnancy
Missing information	Treatment of influenza in immunocompromised patients

II.B SUMMARY OF IMPORTANT RISKS

Important identified risk: Development of oseltamivir-induced viral resistance	
Evidence for linking the risk to the medicine	Resistance Update Report, October 2008 (RDR1031296); publication by the ISIRV-AVG [Periodic safety update report (PSUR) 1030174]; Influenza Resistance Information Study NV20237E (IRIS) Clinical study report (CSR) (RDR 1058241, 1064482, 1069158).
Risk factors and risk groups	Data suggest that children are at a greater risk of developing resistance compared with adults. The higher proportion of children found to harbor resistant virus could be related to higher viral titers or longer duration of viral shedding. The prolonged period of viral replication in young children allows a greater potential for the selective pressure exerted by neuraminidase inhibitor therapy to result in emergence of resistant virus. These factors are probably related to the children's lack of prior exposure to influenza and their consequently naïve immune system. Unit-based dosing has been shown to provide more adequate exposure in children as compared to weight-based dosing. Weight-based dosing is therefore considered an additional risk factor for children. Younger children have a higher rate of renal clearance than adults. The unit-based dosing regimen approved for children aged 1-12 in the EU compensates for this pharmacokinetic difference by providing greater doses relative to weight in the younger age bracket. In contrast, a weight-based dosing schedule has been approved in Japan. In addition, Japanese children historically also only received around 3 days of treatment versus the 5 days recommended duration of treatment. The combination of lower exposures and shorter duration of therapy in Japanese children may represent a risk factor leading to increased selection of viral variants with reduced drug susceptibility. Immunocompromised patients, both adults and children also represent a particularly vulnerable group who can exhibit prolonged periods of viral shedding and resistance can occur with a higher frequency than in immune competent individuals.

Important identified risk: Development of oseltamivir-induced viral resistance	
Risk minimization measures	**Routine risk communication:** SmPC**:** Section 5.1 (Pharmacodynamic properties) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Tamiflu is subject to medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risk: Exposure during pregnancy	
Evidence for linking the risk to the medicine	While no controlled clinical studies have been conducted on the use of oseltamivir in pregnant women, there is a large amount of data available from post-marketing and retrospective observational surveillance data (more than 1000 exposed outcomes during the first trimester), which indicate no malformative nor feto/neonatal toxicity (Tanaka et al. 2009; Greer et al. 2010; Svensson et al. 2011; Varner et al. 2011; Saito et al. 2013; Beau et al. 2014; Dunstan et al. 2014; Graner et al. 2017). However, in one observational study (BV29684, Final Clinical Study Report 1076146, January 2017), while the overall malformation risk was not increased, the results for major congenital heart defects diagnosed within 12 months of birth were not conclusive. In this study, the rate of major congenital heart defects following oseltamivir exposure during the first trimester was 1.76% (7 infants out of 397 pregnancies) compared to 1.01% in unexposed pregnancies from the general population (Odds Ratio 1.75, 95% Confidence Interval 0.51 to 5.98, not statistically significant). This study was too small to reliably assess individual types of major malformations; moreover women exposed to oseltamivir and women

Important potential risk: Exposure during pregnancy	
	unexposed could not be made fully comparable, in particular whether or not they had influenza.
Risk factors and risk groups	Women of child-bearing potential.
Risk minimization measures	**Routine risk communication:** SmPC: Section 4.6 (Fertility,pregnancy and lactation) Section 5.1 (Pharmacodynamic properties) Section 5.2 (Pharmacokinetic properties) **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Tamiflu is subject to medical prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing information: Treatment of influenza in immunocompromised patients	
Risk minimization measures	**Routine risk communication:** SmPC**:** Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Section 5.1 (Pharmacodynamic properties) Section 5.2 (Pharmacokinetic properties) **Routine risk minimization activities recommending specific clinical measures to address the risk**: None **Other risk minimization measures beyond the Product Information**: Medicine's legal status: Tamiflu is subject to medical

	prescription. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** NV25719 See Section II.C of this summary for an overview of the post-authorization development plan.

II.C POST-AUTHORIZATION DEVELOPMENT PLAN

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Tamiflu.

II.C.2 Other studies in post-authorization development plan

Study short name: NV25719

Purpose of the study: The objective of this study is:

- To estimate the exposure achieved with each of different dose levels of oseltamivir through the application of an established population PK model to the sparse concentration data generated.
- To examine the duration of treatment, of viral shedding, and of fever and to examine the safety, tolerability, incidence of influenza-associated complications and of resistance observed with different doses and duration of treatment and characterize any resistant virus isolate in terms of sequence and phenotype.